Title

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Journal

Annals of surgical oncology, 27(9)

ISSN

1068-9265

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Publication Date

2020-09-01

DOI

10.1245/s10434-020-08466-x

Peer reviewed

Author Reflection: Prognostic Utility of Pre- and Postoperative Circulating Tumor DNA Liquid Biopsies in Patients with Peritoneal Metastases

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Financial support: Funded in part by National Cancer Institute grant P30 CA023100 and the Joan and Irwin Jacobs Fund philanthropic fund. Study also funded in part by Guardant Health (Guardant Health, Inc., Redwood City, CA). The project described was partially supported by the National Institutes of Health, Grant TL1TR001443 of CTSA funding beginning August 13, 2015 and beyond. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Disclosures:
Razelle Kurzrock discloses Stock and Other Equity Interests (IDbyDNA, CureMatch, Inc., and Soluventis); Consulting or Advisory Role (Gaido, LOXO, X-Biotech, Actuate Therapeutics, Roche, NeoMed, Soluventis, and Pfizer); Speaker's fee (Roche); Research Funding (Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, Konica Minolta, DeBiopharm, Boerhringer Ingelheim, and OmniSeq [All institutional]); Board Member (CureMatch, Inc). Paul Riviere discloses consulting fees from Peptide Logic, LLC.

Past

The peritoneum is a potential site of metastasis in virtually all pelvic and abdominal malignancies. Surgical treatment with debulking or complete cytoreduction with or without hyperthermic intraperitoneal chemotherapy (HIPEC) can provide palliation of symptoms and potentially, survival advantages over other treatments. However, radiographic identification of residual or recurrent peritoneal disease is challenging.[1,2] A biomarker which could identify residual or recurrent disease might provide improved postoperative risk stratification and surveillance assessments. Cell-free circulating tumor DNA (ctDNA) shed from tumor is measurable in plasma and provides both quantitative and qualitative data that can be assessed non-invasively over time. We have previously found that ctDNA liquid biopsy is a preoperative prognosticator after surgical resection of peritoneal metastases,[3] but questions remain about its utility for risk stratification and surveillance in the postoperative setting.

Present

As demonstrated in our study,[4] there are specific postoperative ctDNA findings that have clear implications for progression and prognosis, such as development of a new clonal population (i.e. the detection of new alterations by ctDNA, distinct from the prior detected mutational profile). However, the detection of early postoperative ctDNA is not an independent predictor of worse progression-free survival, in our somewhat limited cohort. Additionally,

it appears that the peritoneum may be relatively sequestered with regards to systemic blood ctDNA detection: tumors types with a low rate of detection preoperatively have a much higher rate of detection postoperatively, despite having well-characterized mutations that would be detectable in plasma.

Future

While ctDNA sequencing has shown promise for surveillance after definitive local therapies in other contexts,[5] its implementation in metastatic disease to the peritoneum may require a more nuanced approach. Our findings suggest that detection of ctDNA is the sum of numerous effects; some known (e.g. surgical removal of locoregional disease, a fixed gene panel), some suspected (e.g. a blood-peritoneal ctDNA barrier), and likely many more unknown. Questions of chronicity appear to be critical to implementation of these assays after surgery for peritoneal metastases. What is the ideal delay after surgery to assess ctDNA response? What is the effect of intraoperative chemotherapy? Does the observed blood-peritoneal barrier recover postoperatively, and if so, over what time? Should ctDNA be followed longitudinally? A larger clinical trial of serial ctDNA analysis in patients undergoing resection of peritoneal metastases is the obvious next step to translate this technology into clinical utility.

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